Original Research Article

Glycaemic control and C- reactive protein levels in type 2 diabetes mellitus -how well they co-relate?: a prospective study

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ABSTRACT

Background: Poorly controlled diabetes mellitus as indicated by elevated glycated haemoglobin (HbA1c) levels is associated with increased cardiovascular risk. C–reactive protein (CRP), an important cardiovascular risk factor, is elevated in diabetics with poor glycaemic control than those with good control. The present study assessed the correlation between HbA1c and CRP levels.

Methods: A prospective study was conducted in thirty type 2 diabetic patients irrespective of the disease duration and treatment; those with established target organ damage were excluded. HbA1c and hsCRP levels were measured at baseline; sugars were monitored monthly and medications optimised; at the end of six months HbA1c and hsCRP levels were measured.

Results: Mean age of the study subjects was 58.7 ± 8.6 years; At the baseline, all had poor glycaemic control (HbA1c >7%); 15 had hsCRP >3 mg/L. At the end of 6 months, 5 achieved good glycaemic control (HbA1c <7%); 10 had hsCRP >3 mg/L. Baseline median hsCRP was 3.33 mg/L (0.68, 15.9) and at the end of 6 months it was 2.08 mg/L (0.48, 9.12). Mean HbA1c at baseline and end line was $10.6 \pm 1.55\%$ and $8.43 \pm 1.84\%$ respectively. There was significant reduction in both the mean HbA1c and median hsCRP at the end of 6 months (p <0.001). Positive correlation was observed between HbA1c and CRP at baseline (r=0.32, p=0.10). However, this was not observed at the end of 6 months.

Conclusions: There is positive correlation between the level of glycaemic control (HbA1c) and CRP levels; Better glycaemic control results in significant reduction in the hsCRP levels.

Keywords: C-reactive protein, Correlation, Glycaemic control, hsCRP, HbA1c

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by the defects in insulin secretion or action; chronic hyperglycaemia can lead to microvascular and macrovascular complications if the blood sugars are not under optimal control. The glycaemic control is assessed by the measurement of glycated haemoglobin (HbA1c) which has its own advantages and disadvantages.[1] Till date HbA1c is the widely used tool to assess the glycaemic status. Poor glycaemic control as indicated by

elevated HbA1c levels accelerates the atherosclerosis process and significantly increases the risk of cardiovascular events.[2] C-reactive protein measured by highly sensitive assays (hsCRP), is a very sensitive marker of the inflammatory activity in the arterial wall.[3,4] It is an important predictor of cardiovascular risk apart from the traditional risk factors.[5,6] It is interesting to note that chronic hyperglycaemia stimulates the release of various inflammatory cytokines (IL 6; TNF α) and induces the secretion of acute phase reactants by liver, which in turn results in elevation of CRP in association

with elevated fasting plasma glucose.[7] Studies had shown that elevated CRP levels is associated with an increased risk of future development of diabetes mellitus.[8] Also, people with diabetes mellitus had elevated levels of CRP than non -diabetics.[9,10] We understand that both chronic systemic inflammation and hyperglycaemia contribute to the development and progression of atherosclerotic cardiovascular disease. Experimental and clinical studies have confirmed the inter-relationship between CRP, hyperglycaemia and atherosclerosis.[11,12] In states of elevated CRP, hyperglycaemia exaggerates the pro-atherogenic effects of CRP.[12,13] Few studies which had assessed the relationship between CRP levels and the level of glycaemic status showed conflicting results; some studies had proven the positive co-relation between glycaemic control and CRP levels.[14-16] while some failed to do so.[6] Also, the effect of good glycaemic control on CRP levels is not clear. The aim of this study is to determine the co-relation of glycaemic control as measured by HbA1c levels with hsCRP in patients with type 2 diabetes mellitus and to determine if better glycaemic control reduces CRP levels.

METHODS

The study was conducted in the Department of Medicine, PSG Institute of Medical Sciences, Coimbatore. Patients with type 2 diabetes mellitus diagnosed on the basis of WHO criteria were prospectively enrolled in the study from September 2014 to May 2015 irrespective of disease duration and treatment. Patients with established cardiovascular disease, chronic kidney disease, infections, haemolytic anaemia, on drug therapy with statins and non-steroidal anti -inflammatory drugs were excluded from the study. The study was approved by the Institutional Ethics Committee (approval number: 14/184); informed consent was obtained from all the study participants.

At the time of enrolment in the study, blood samples were collected from the participants for measurement of HbA1c and hsCRP levels. HbA1c was measured by high pressure liquid chromatography (Variant II Turbo - HbA1c kit - 2.0). High sensitive CRP was measured by particle enhanced turbidometry assay (Cobas Integra 400 plus). They were followed up on a monthly basis, clinical evaluation was done; fasting and postprandial blood sugars were monitored and adjustment of anti-diabetic medications done on an individual basis in addition to re-enforcement on life style modification (diet and exercise). At 6 months, blood samples were collected for HbA1c and CRP levels.

Statistical analysis

Descriptive statistics were reported as mean ± SD for normally distributed data, median with 25th and 75th for the non-normal data. Paired t test or Wilcoxon Signed rank test was used to test the significance for the change in HBA1c and CRP after 6 months from baseline.

Spearman's Rank correlation is used to assess the correlation between the variables. P value less than 5% was considered statistically significant. All the analyses were done using SPSS version 23.0.

RESULTS

Among the 30 subjects studied, 70% of people were between the age group of 50-70 years; the mean age of the study subjects was 58.7±8.6 years; there were 17 females (57%) and 13 males (43%).
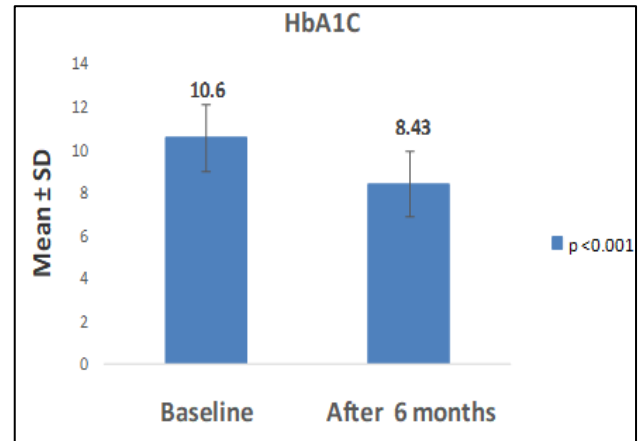
Figure 1: Mean HbA1c levels in % at baseline and at the end of 6 months.
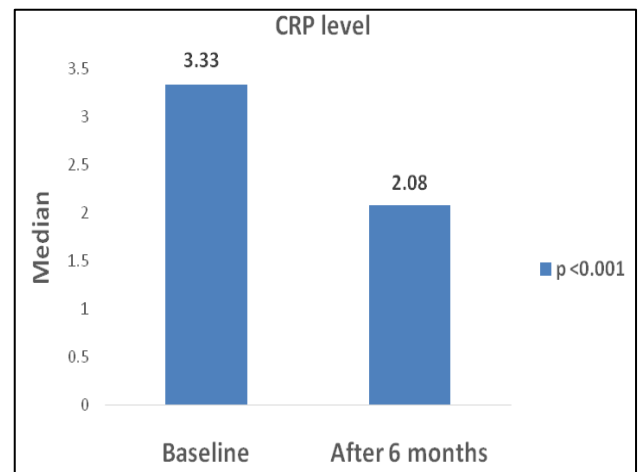
Figure 2: Median CRP levels in mg/L at baseline and at the end of 6 months.

At the baseline, all of them had poor glycaemic control (HbA1c >7%); 15 had hs CRP >3 mg/L. At the end of 6 months, 6 patients lost to follow up; HbA1c and hsCRP levels were measured for the remaining subjects; 5 achieved good glycaemic control (HbA1c <7%); 10 had hs CRP >3 mg/L. The mean hsCRP at baseline and at the end of 6 months was 7.85±9.75 and 4.88 ±5.41 mg/L respectively. Baseline median hsCRP was 3.33 (0.68, 15.9) and at the end of 6 months it was 2.08 (0.48, 9.12). The mean HbA1c at baseline and end line was

10.6±1.55% and 8.43±1.84% respectively. There was statistically significant reduction in both the mean HbA1c and median hsCRP values at the end of 6 months with effective individual based anti-diabetic treatment (p <0.001). The results are depicted in Figure 1 and 2. Positive co-relation was observed between HbA1c and CRP at baseline (r=0.32, p=0.10) although it was not statistically significant. However, this correlation was not observed at the end of 6 months.

DISCUSSION

The role of chronic low-grade inflammation contributing to the pathogenesis of diabetes and its related complications is well known. Chronic hyperglycaemia induces oxidative stress and chronic inflammatory state, which jointly contribute to the pathogenesis of atherosclerosis. C-reactive protein levels more than 3.0 mg/L is associated with worse cardiovascular outcome.[17] Various studies had demonstrated significantly elevated serum hsCRP levels in diabetics than non-diabetics.[15,16,18] Also, significant elevation was noted in those with poor glycaemic control compared to those with good glycaemic control.[15] Recent research has shown that HbA1c and CRP jointly contribute to the increased cardiovascular risk in patients with advanced cardiovascular disease.[19]

The mean hsCRP levels in the study population at baseline was 7.85±9.75 mg/l which is in accordance to that observed in another Indian study conducted in Bangalore (6.9±9.3 mg/l); while Saudi Arabian and Bangladesh studies had shown mean hsCRP levels lower than that observed in the present study, 1.13 and 2.3 mg/L respectively.[6,18] The reason for this difference in CRP levels is unclear; further studies are needed to assess the differences in ethnic groups; standardisation of the techniques used for measurement of hsCRP.

A positive co-relation was observed between HbA1c and hsCRP levels at the baseline in the present study indicating that the change in HbA1c affects hsCRP levels in the same direction. There are other studies which support our results. In a cross-sectional study conducted by Gohel et al, a significant positive linear relationship was observed between hsCRP and HbA1c.[15] Li et al, Khan DA et al, and Sarinnapakorn V et al, also had made similar observation in their studies.[20-22] Kashinakunti et al, in their case control study noted significantly high hsCRP levels in diabetics than controls; also noted positive co-relation between hsCRP and HbA1c, although non-significant.[16] Low HbA1c levels strongly related to negative hs-CRP levels as observed by Amanullah S et al.[23] Another study conducted in Sudan showed significant correlation between CRP levels with fasting plasma glucose and HbA1c.[24] All the above-mentioned studies were cross-sectional observational studies which assessed the relationship between Hba1c and CRP.

On literature search authors could find only one study conducted in Mexico which had assessed prospectively the effects of good glycaemic control on the CRP levels. The study was conducted on newly diagnosed type 2 diabetes patients; they were followed up for 6 months by intensive blood sugar management. There was significant reduction in HbA1c from baseline value of 13.0±4.9 to 8.9±2.9% at the end of 6 months, p <0.00001 which resulted in significant reduction in hsCRP levels (9.6±6.2 to 6.3±3.0 mg/l, p <0.00001). The present study also had shown similar results; significant reduction in hsCRP levels at the end of 6 months compared to baseline was observed following better glycaemic control and reduction in HbA1c levels. In that study, although glycaemic control was achieved in 71 patients at the end of 6 months, only 29 (40.8%) of them showed a reduction in CRP levels to 3 mg/l or less and the remaining 42 (59.2%) maintained a high CRP level. The study concluded that CRP is moderately influenced by glycaemic control.[25] Similar to that observation, the present study also showed that only 41.6% of the study subjects achieved CRP levels <3 mg/L by 6 months.

The positive co-relation observed between HbA1c and CRP at the baseline was not observed at 6 months; this may be because CRP is moderately influenced by glycaemic control.25 There are other variables which affect CRP levels like age, gender, body weight, LDL cholesterol levels. The present study did not take into considerations those variables which is a limitation of the present study.

CONCLUSION

There is positive correlation between the level of glycemic control (HbA1c) and CRP levels; Better glycemic control results in significant reduction in the hsCRP levels.

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